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RADIATION RESEARCH 114, 42–53 (1988)

Implication of Prostaglandins and Histamine H_1 and H_2 Receptors in Radiation-Induced Temperature Responses of Rats

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KANDASAMY, S. B., HUNT, W. A., AND MICKLEY, G. A. Implications of Prostaglandins and Histamine H_1 and H_2 Receptors in Radiation-Induced Temperature Responses of Rats. *Radiat. Res.* **114**, 42–53 (1988).

Exposure of rats to 1–15 Gy γ radiation (^{60}Co) induced hyperthermia, whereas 20–200 Gy induced hypothermia. Exposure either to the head or to the whole body to 10 Gy induced hyperthermia, while body-only exposure produced hypothermia. This observation indicates that radiation-induced fever is a result of a direct effect on the brain. The hyperthermia due to 10 Gy was significantly attenuated by the pre- or post-treatment with a cyclooxygenase inhibitor, indomethacin. Hyperthermia was also altered by the central administration of a μ-receptor antagonist naloxone but only at low doses of radiation. These findings suggest that radiation-induced hyperthermia may be mediated through the synthesis and release of prostaglandins in the brain and to a lesser extent to the release of endogenous opioid peptides. The release of histamine acting on H_1 and H_2 receptors may be involved in radiation-induced hypothermia, since both the H_1 receptor antagonist, mepyramine, and H_2 receptor antagonist, cimetidine, antagonized the hypothermia. The results of these studies suggest that the release of neurohumoral substances induced by exposure to ionizing radiation is dose dependent and has different consequences on physiological processes such as the regulation of body temperature. Furthermore, the antagonism of radiation-induced hyperthermia by indomethacin may have potential therapeutic implications in the treatment of fever resulting from accidental irradiations.

Exposure to ionizing radiation can interfere with the regulation of body temperature. Hyperthermia has been observed after exposure to ionizing radiation in a number of species including rabbits, cats, and humans (*1–3*). This effect is thought to result from actions on the neuroregulatory centers in the hypothalamus, since the response can be prevented by pretreatment with the centrally acting antipyretic, aminopyrine (*1*). In addition, preliminary evidence from our laboratory suggests that radiation can also induce hypothermia in rats and guinea pigs (*4, 5*). However, the mechanisms underlying these effects are unknown.

Normal thermoregulation apparently is controlled by a variety of putative mediators. Initially, the monoamine neurotransmitters were implicated in thermoregulation, but this view is incompatible with empirical findings that have shown that the effect of monoamines on body temperature varies from species to species (*6*). Prostaglandins of the E series, on the other hand, induce an increase in body temperature in all the mammalian species investigated so far (*7, 8*). In addition, a variety of endog-

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enous peptides capable of producing opiate-like effects have been isolated from brain tissue and have been implicated in thermoregulation (*9–12*).

Exposure to ionizing radiation has been reported to increase blood levels of histamine in humans undergoing radiation therapy, as well as in dogs following irradiation (*13–15*). Histamine has been implicated in radiation-induced hypotension (*16*), reductions in cerebral blood flow (*17*), and performance decrements (*18*). Histamine is present in high concentration in the hypothalamus (*19, 20*) and is localized in nerve terminals (*21*). Also, ascending histamine tracts are found in the median forebrain bundle (*22*); histidine decarboxylase, the enzyme that converts histidine to histamine, is localized in different regions of the brain (*23*); histamine activates adenylate cyclase in the brain (*24*); and brain histamine turnover is increased by stress (*25*). Administration of histidine systemically (*26*) or histamine centrally (*27–29*) evokes hypothermia due to both H_1 and H_2 receptor activation (*30*). These neurochemical and pharmacological studies suggest that histamine may be a central neurotransmitter involved in many physiological functions including thermoregulation and could underlie radiation-induced hypothermia.

The purpose of the present study was to characterize the effect of exposure to ionizing radiation on body temperature in the rat (a) by determining the effect of variable doses of radiation on body temperature, (b) by determining whether radiation is acting on the brain or peripheral sites, and (c) by then elucidating possible mechanisms involved in these temperature responses.

MATERIALS AND METHODS

Drugs used. Indomethacin and serotonin creatinine sulfate (Sigma Chemical Co., St. Louis, MO); naloxone (National Institute on Drug Abuse, Washington, DC); mepyramine maleate (Mallinckrodt, Inc., St. Louis, MO); methysergide maleate (Sandoz Pharmaceuticals, E. Hanover, NJ); 2-methylhistamine dihydrochloride, 4-methylhistamine dihydrochloride, and cimetidine (Smith Kline French Laboratory, Philadelphia, PA); ketamine hydrochloride (Parke-Davis, Detroit, MI); xylazine (Hayer-Lockhart, Shawnee, KS); acepromazine (Ayerst Laboratories, NY). 2-methylhistamine, 4-methylhistamine, mepyramine, naloxone, and serotonin were dissolved in sterile, nonpyrogenic saline. Indomethacin was dissolved in a mixture of 1% sodium hydroxide and saline, while methysergide was dissolved in 10% dimethyl sulfoxide (DMSO) and pyrogen-free distilled water. Cimetidine was dissolved in 0.1 ml of 1 *N* HCl and diluted to the final volume with saline.

Animals. Male Sprague-Dawley Crl:CD(SD)BR rats (Charles River Breeding Laboratories, Kingston, NY) weighing 200–300 g were used in these experiments. Rats were quarantined on arrival and screened for evidence of disease by serology and histopathology before being released from quarantine. The rats were housed individually in polycarbonate isolator cages (Lab Products, Maywood, NJ) on autoclaved hardwood contact bedding (Beta Chip Northeastern Products Corp., Warrensburg, NY) and acidified water (pH 2.5 using HCl) *ad libitum*. Animal holding rooms were kept at 21 ± 1°C with 50 ± 10% relative humidity on a 12-h light:dark lighting cycle with no twilight.

Radiation exposure. Male Sprague–Dawley rats weighing 200–300 g were used in these experiments. The rats were placed in clear plastic containers for approximately 5 min before irradiation or sham exposure. The animals were exposed bilaterally to varying doses of γ photons using a ^{60}Co source at a rate of 10 or 20 Gy/min. Shielding of the head or body was accomplished using lead bricks. Dosimetry was performed using paired 50-ml ion chambers. Delivered dose was expressed as a ratio of the dose measured in a tissue-equivalent plastic phantom enclosed in a restraining tube to that measured in air.

Central administration of drugs. Rats were anesthetized with 1 ml/kg, im of a mixture of ketamine (50 mg/kg), xylazine (5 mg/kg), and acepromazine (1 mg/kg), and were placed in a rat stereotaxic apparatus (David Kopf Instruments, No. 320). A single cannula was inserted into the lateral ventricle according to coordinates derived from the atlas of Pelligrino *et al.* (*31*): 0.8 mm posterior to bregma, 2.5 mm lateral.

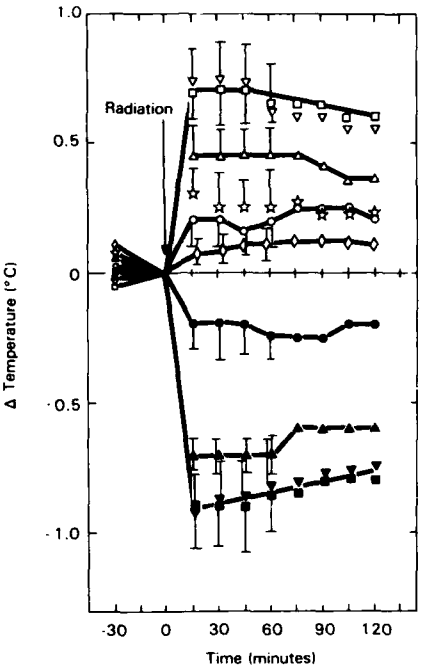

FIG. 1. Changes in rectal temperature of rats exposed to variable doses of ionizing radiation: Sham radiation (◇), 1 Gy (○), 3 Gy (☆), 5 Gy (△), 10 Gy (□), 15 Gy (▽), 20 Gy (●), 50 Gy (▲), 100 Gy (▼), 150 Gy (■). Each point represents the mean ± SE of five observations except (◇) and (□) which represent 15 observations. Zero on the abscissa represents body temperature at the time of injection.

The cannula was lowered until cerebrospinal fluid rose in the cannula. Dental acrylic was used to secure the cannula. After the end of an experiment, injection sites were histologically verified. The volume of injection was always 10 μl. At least 1 week was allowed for recovery before animals were used for experiments. Injections/radiation were done at the same time of day (0900) to avoid diurnal variation in temperature. The antagonists (indomethacin, naloxone, mepyramine, cimetidine, and methysergide) were given 30 min before the administration of the radiation/agonists (2-methylhistamine, 4-methylhistamine, or serotonin).

Measurement of body temperature. The animals were placed in cages 1 h before the beginning of experiments that were carried out at an environmental temperature of 22 ± 1°C. Body temperature was measured every 15 min over 2 h with thermistor probes inserted approximately 6 cm into the rectum and connected to a datalogger (Minitrend 205).

Statistics. Statistical evaluations were undertaken using Student's t test with a significance level of $P < 0.05$.

RESULTS

Exposure of rats to 1–15 Gy γ radiation induced hyperthermia, whereas 20 to 200 Gy induced hypothermia (Fig. 1). The onset of these effects was rapid and they reached their maximum effect within 15 min. The exposed rats normally did not show any significant behavioral changes up to 100 Gy but started circling (two of six

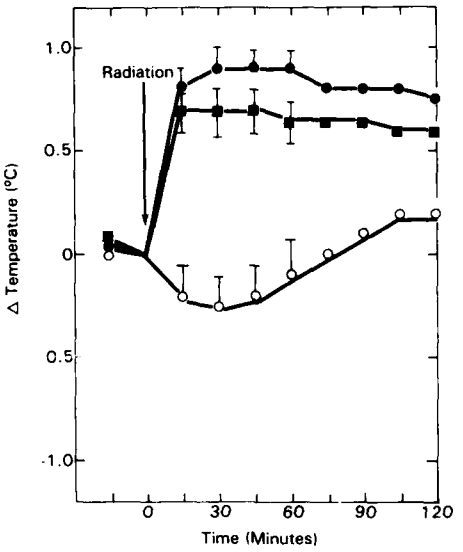

FIG. 2. Effect of 10 Gy ionizing radiation on body only (○), whole body (■), and head only (●). Each point represents the mean ± SE of six observations. Zero on the abscissa represents body temperature at the time of irradiation.

rats) when they were exposed above 100 Gy. On the basis of these results, a 10-Gy dose of radiation was used to determine the site of action of the effects of radiation on body temperature.

As can be seen in Fig. 2, hyperthermia induced by a 10-Gy dose of γ radiation occurred only after whole-body or head-only exposure, not when the head was shielded. Since whole-body exposure resulted in the same effect as head-only exposure, subsequent studies used whole-body exposure to ionizing radiation.

Experiments were then undertaken to determine what mechanisms may underlie radiation-induced changes in body temperature by comparing to radiation the effects of drugs with known actions and by determining if antagonists to these drugs could block the effects of radiation.

Since prostaglandins induced hyperthermia (*7, 8*), the effect of indomethacin, an inhibitor of prostaglandin synthesis, on hyperthermia induced by ionizing radiation was examined. Pretreatment with 1–5 mg/kg (ip) of indomethacin inhibited in a dose-dependent manner the hyperthermia induced by 1–15 Gy γ photons (Fig. 3 and Table I). Indomethacin alone had no effect on body temperature (Fig. 3). In addition, 1 mg/kg, ip, of indomethacin (given immediately after determination of body temperature 15 min after irradiation) rapidly reversed the fever produced by irradiation (Fig. 4).

The effect of pretreatment of naloxone on hyperthermia induced by ionizing radiation was also determined. Naloxone (10–50 μg, icv) had no significant effect on the body temperature in control animals but attenuated the hyperthermia only at doses

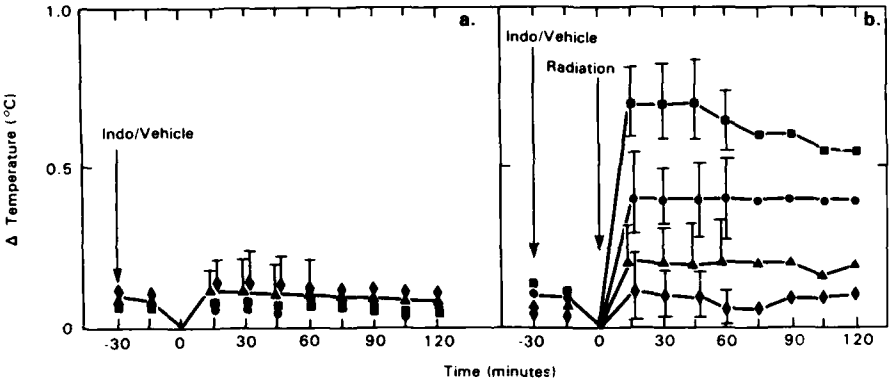

FIG. 3. Effect of intraperitoneal injection of indomethacin on hyperthermia induced by 10 Gy ionizing radiation. (a) Indomethacin (Indo) 1 mg/kg (▲), 3 mg/kg (■), 5 mg/kg (●), vehicle (♦); (b) 10 Gy ionizing radiation alone (■) and in the presence of Indo 1 mg/kg (●), 3 mg/kg (▲), and 5 mg/kg (♦). Each point represents mean ± SE of five observations. Zero on the abscissa represents temperature at the time of second injection.

of 1–3 Gy (Table II). The hyperthermia due to 5 to 15 Gy radiation was resistant to 10–100 μg, icv, of naloxone (Fig. 5 and Table II). Doses of naloxone above 100 μg were not used, since they induce hyperthermia in control animals.

Since histamine is released after exposure to radiation, its possible role in the thermoregulatory effects of radiation was examined. To differentiate between actions on

TABLE I

Effect of Indomethacin on the Hyperthermia Induced by Exposure to Ionizing Radiation

Treatment		*Mean change temperature (°C)*
Vehicle	+ 1 Gy ionizing radiation	0.3 ± 0.10 (n = 8)[a]
Indomethacin, 1 mg/kg	+ 1 Gy ionizing radiation	0.1 ± 0.10 (n = 5)
Indomethacin, 3 mg/kg	+ 1 Gy ionizing radiation	−0.1 ± 0.15 (n = 5)
Indomethacin, 5 mg/kg	+ 1 Gy ionizing radiation	−0.2 ± 0.20 (n = 5)
Vehicle	+ 5 Gy ionizing radiation	0.6 ± 0.12 (n = 8)
Indomethacin, 1 mg/kg	+ 5 Gy ionizing radiation	0.1 ± 0.12 (n = 5)*
Indomethacin, 3 mg/kg	+ 5 Gy ionizing radiation	−0.1 ± 0.20 (n = 5)*
Indomethacin, 5 mg/kg	+ 5 Gy ionizing radiation	−0.2 ± 0.15 (n = 5)*
Vehicle	+ 15 Gy ionizing radiation	0.8 ± 0.15 (n = 5)
Indomethacin, 1 mg/kg	+ 15 Gy ionizing radiation	0.3 ± 0.20 (n = 5)**
Indomethacin, 3 mg/kg	+ 15 Gy ionizing radiation	0.2 ± 0.10 (n = 5)**
Indomethacin, 5 mg/kg	+ 15 Gy ionizing radiation	0.1 ± 0.20 (n = 5)**

[a] n = number of animals.

* Significantly different from 5 Gy ionizing radiation; $P < 0.05$.

** Significantly different from 15 Gy ionizing radiation; $P < 0.05$.

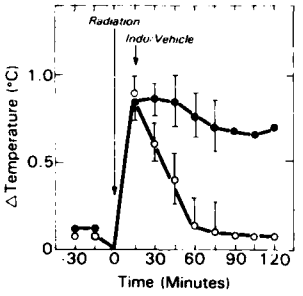

FIG. 4. Effect of intraperitoneal injection of indomethacin on hyperthermia induced by 10 Gy ionizing radiation: ionizing radiation alone (●) and in the presence of indomethacin (Indo) 1 mg/kg (○). Each point represents the mean ± SE of five observations. Zero on the abscissa represents temperature before radiation. At the second arrow Indo/vehicle was administered.

H_1 and H_2 receptors, agonists and antagonists specific for these receptors were used. Mepyramine (10–30 μg, icv), an H_1 antagonist, and cimetidine (10–30 μg, icv), an H_2 antagonist, both of which were previously found to antagonize hypothermia in-

TABLE II

Effect of Naloxone on the Hyperthermia Induced by Exposure to Ionizing Radiation

Treatment		*Mean change temperature (°C)*
Saline	+ 1 Gy ionizing radiation	0.3 ± 0.05 (n = 10)
Naloxone, 10 μg	+ 1 Gy ionizing radiation	0.1 ± 0.10 (n = 7)*
Naloxone, 30 μg	+ 1 Gy ionizing radiation	−0.1 ± 0.15 (n = 7)*
Naloxone, 50 μg	+ 1 Gy ionizing radiation	−0.1 ± 0.10 (n = 7)*
Saline	+ 3 Gy ionizing radiation	0.4 ± 0.10 (n = 8)
Naloxone, 10 μg	+ 3 Gy ionizing radiation	0.2 ± 0.10 (n = 7)**
Naloxone, 30 μg	+ 3 Gy ionizing radiation	0.1 ± 0.10 (n = 7)**
Naloxone, 50 μg	+ 3 Gy ionizing radiation	−0.1 ± 0.15 (n = 7)**
Saline	+ 5 Gy ionizing radiation	0.5 ± 0.15 (n = 6)
Naloxone, 10 μg	+ 5 Gy ionizing radiation	0.7 ± 0.25 (n = 5)
Naloxone, 30 μg	+ 5 Gy ionizing radiation	0.7 ± 0.15 (n = 5)
Naloxone, 50 μg	+ 5 Gy ionizing radiation	0.6 ± 0.10 (n = 5)
Saline	+ 10 Gy ionizing radiation	0.7 ± 0.15 (n = 5)
Naloxone, 100 μg	+ 10 Gy ionizing radiation	0.9 ± 0.25 (n = 5)
Saline	+ 15 Gy ionizing radiation	0.8 ± 0.15 (n = 5)
Naloxone, 10 μg	+ 15 Gy ionizing radiation	0.9 ± 0.20 (n = 5)
Naloxone, 30 μg	+ 15 Gy ionizing radiation	0.8 ± 0.10 (n = 5)
Naloxone, 50 μg	+ 15 Gy ionizing radiation	1.0 ± 0.15 (n = 5)
Naloxone, 100 μg	+ 15 Gy ionizing radiation	1.1 ± 0.20 (n = 5)

* Significantly different from 1 Gy ionizing radiation; $P < 0.05$.
** Significantly different from 3 Gy ionizing radiation; $P < 0.05$.

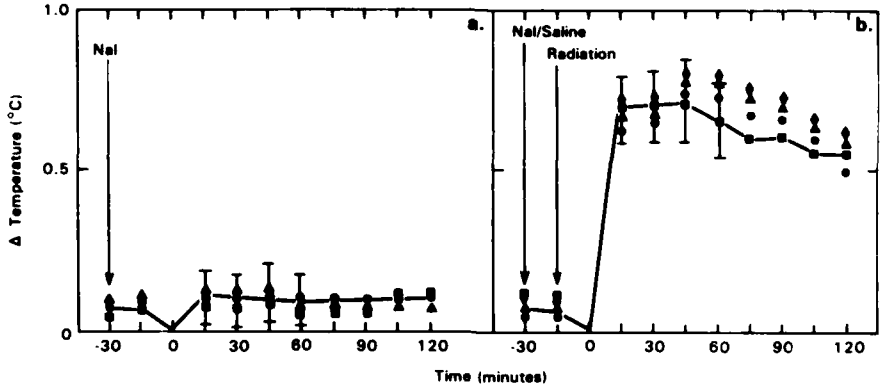

FIG. 5. Effect of icv naloxone on hyperthermia induced by 10 Gy ionizing radiation. (a) Naloxone (Nal) 10 μg (▲), 30 μg (●), and 50 μg (■); (b) 10 Gy ionizing radiation alone (■) and in the presence of Nal 10 μg (◆), 30 μg (▲), and 50 μg (●). Each point represents mean ± SE of five observations. Zero on the abscissa represents temperature at the time of second injection.

duced by histamine in guinea pigs (32), significantly antagonized in a dose-dependent manner hypothermia induced by exposure to 50 Gy radiation (Figs. 6 and 7). In addition, mepyramine antagonized hypothermia induced by 2-methylhistamine (10 μg, icv), an H_1 agonist, but did not antagonize the hypothermia induced by 4-methylhistamine (50 μg, icv), an H_2 agonist (Fig. 6 and Table III). Likewise, cimetidine significantly attenuated the hypothermia induced by 4-methylhistamine but not that induced by 2-methylhistamine (10 μg, icv) (Fig. 7 and Table III).

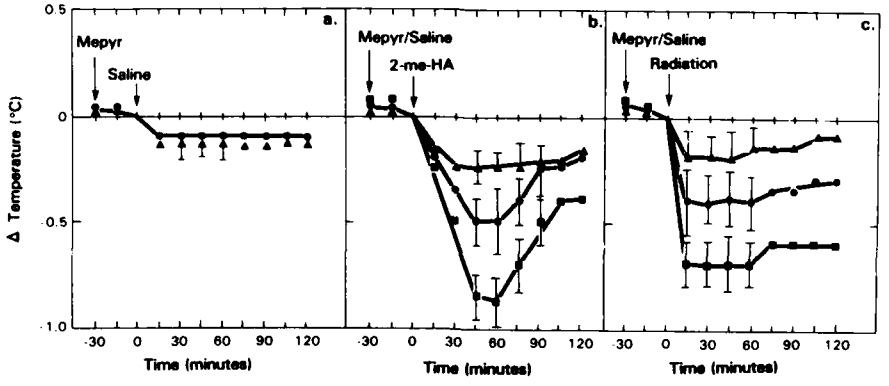

FIG. 6. Effect of icv mepyramine on hypothermia induced by 2-methylhistamine and ionizing radiation. (a) Mepyramine (Mepyr) 10 μg (●) and 30 μg (▲); (b) 10 μg of 2-methylhistamine (2-me-HA) alone (■) and in the presence of Mepyr 10 μg (●) and 30 μg (▲); (c) 50 Gy ionizing radiation alone (■) and in the presence of Mepyr 10 μg (●) and 30 μg (▲). Each point represents the mean ± SE of five observations. Zero on the abscissa represents temperature at the time of second injection.

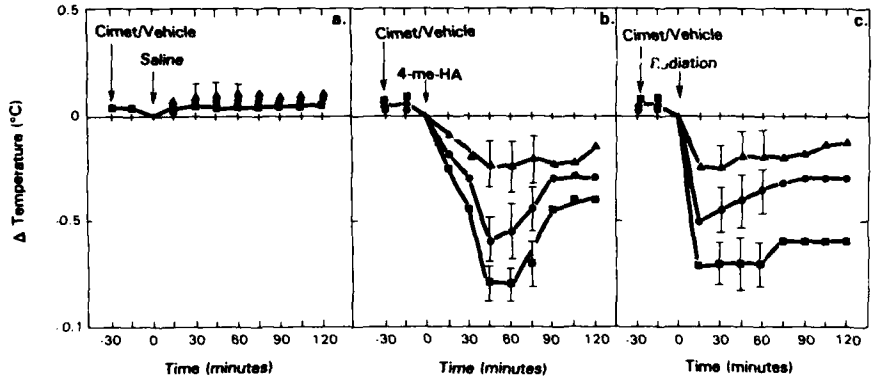

FIG. 7. Effect of icv cimetidine on hypothermia induced by 4-methylhistamine and ionizing radiation. (a) Cimetidine (Cimet) 10 μg (●), 30 μg (■), and vehicle (▲); (b) 30 μg of 4-methylhistamine (4-me-HA) alone (■) and in the presence of Cimet 10 μg (●) and 30 μg (▲); (c) 50 Gy ionizing radiation alone (■) and in the presence of Cimet 10 μg (●) and 30 μg (▲). Each point represents the mean ± SE of five observations. Zero on the abscissa represents temperature at the time of second injection.

Serotonin has also been shown to be involved in thermoregulation (*6*). Serotonin-induced hypothermia (30 μg, icv) can be blocked by pretreatment with the serotonin antagonist methysergide (Fig. 8). However, methysergide had no effect on radiation-induced hypothermia.

DISCUSSION

Exposure of rats to ionizing radiation induced either hyperthermia or hypothermia depending on the dose. Doses of 1–15 Gy γ photons induced hyperthermia, while doses of 20–200 Gy induced hypothermia. Radiation-induced hyperthermia appears to be centrally mediated, since body-only exposure resulted in hypothermia.

Ionizing radiation induces prostaglandin synthesis (*32, 33*). The observations that prostaglandins are potent pyretic agents (*8*) and that various anti-inflammatory

TABLE III

Effect of Mepyramine and Cimetidine on the Hypothermia Induced by 4-Methylhistamine and 2-Methylhistamine

Treatment		*Mean change temperature (°C)*
Saline	+ 4-Methylhistamine	0.8 ± 0.15 (n = 6)
Mepyramine, 10 μg	+ 4-Methylhistamine	0.7 ± 0.20 (n = 5)
Mepyramine, 30 μg	+ 4-Methylhistamine	0.5 ± 0.25 (n = 5)
Saline	+ 2-Methylhistamine	0.9 ± 0.10 (n = 5)
Cimetidine, 10 μg	+ 2-Methylhistamine	1.1 ± 0.25 (n = 5)
Cimetidine, 30 μg	+ 2-Methylhistamine	0.8 ± 0.18 (n = 5)

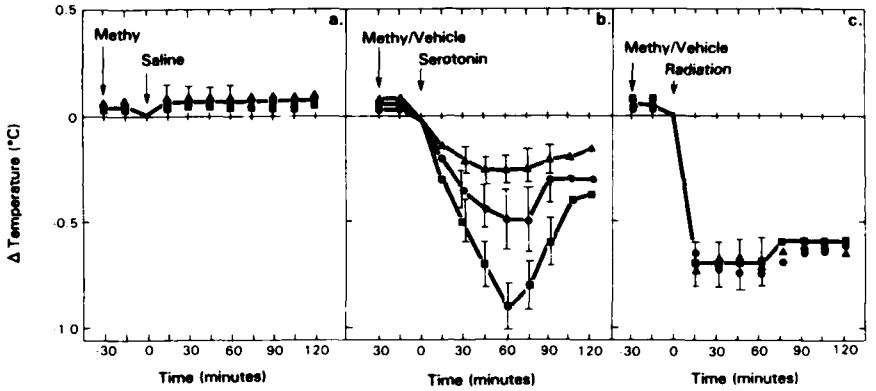

FIG. 8. Effect of icv methysergide on hypothermia induced by serotonin and ionizing radiation. (a) Methysergide (Methy) 10 μg (▲), 30 μg (■), and vehicle (●); (b) 10 μg of serotonin alone (■) and in the presence of Methy 10 μg (●) and 30 μg (▲); (c) 50 Gy ionizing radiation alone (■) and in the presence of Methy 10 μg (●) and 30 μg (▲). Each point represents the mean ± SE of five observations. Zero on the abscissa represents temperature at the time of second injection.

agents blocked their synthesis in tissue (*34*) have implicated prostaglandins in thermoregulation. Indomethacin attenuated the hyperthermia due to low doses of ionizing radiation, indicating that this effect may be mediated by prostaglandins.

Ionizing radiation alters β-endorphin-like immunoreactivity in the brain but not in blood (*35*). β-Endorphin induces hyperthermia. When β-endorphin is injected centrally to different species, varying the ambient temperature and dose, the effect is similar to that observed after central or peripheral administration of morphine (*36, 37*). Relatively low doses of morphine and β-endorphin raise the level about which temperature is regulated in rats, cats, mice, rabbits, guinea pigs, and fish (*38–40*). If radiation induces the release of β-endorphin, naloxone and similar antagonists ought to lower temperature. In our experiments, naloxone attenuated only the hyperthermia induced by 1- and 3-Gy doses of radiation and had no antagonistic effect on higher doses (5 to 15 Gy).

Since indomethacin attenuated the hyperthermia induced by all the lower doses studied, there may be a possible interrelationship between the opioid peptides and prostaglandins. Opioids have been reported to increase the synthesis of prostaglandins in the central nervous system (*41*). If radiation exposure resulted in the release of central β-endorphin, the resulting synthesis and release of prostaglandins would be blocked by indomethacin treatment.

The effect of indomethacin reversing radiation-induced hyperthermia may have some clinical utility. Clinical reports of radiation accidents have consistently indicated the rapid development of fever, lasting for many hours (*42–44*). Patients were generally given antibiotics to suppress infections. Anti-inflammatory drugs, such as indomethacin (a drug used in the treatment of arthritis), have not been used and might be useful adjuncts to therapy. Vomiting and diarrhea are common in accident victims, possibly making indomethacin difficult to administer by the normal oral

route. However, indomethacin could be included in an intravenous drip along with electrolytes and antibiotics.

The hypothermic effect of high doses of radiation appears to involve the release of histamine. Central administration of 2-methylhistamine (a relatively specific H_1 receptor agonist) and 4-methylhistamine (a relatively specific H_2 receptor agonist) caused hypothermia in rats that was selectively attenuated by both the H_1 receptor antagonist, mepyramine, and the H_2 receptor antagonist, cimetidine. Similar results have been reported in guinea pigs and rabbits (*45, 46*). In the present experiments, both mepyramine and cimetidine specifically attenuated the hypothermia induced by 2-methylhistamine and 4-methylhistamine, respectively, and also antagonized radiation-induced hypothermia, indicating the involvement of histaminergic H_1 and H_2 receptors.

Central injection of serotonin in rats induces hypothermia and was specifically antagonized by the serotonin antagonist, methysergide (*47*). However, serotonin was not involved in radiation-induced hypothermia, since methysergide did not attenuate the hypothermia.

The present results indicate that ionizing radiation induces hyperthermia after low doses and hypothermia after high doses. Prostaglandins and to some extent opioid peptides may be involved in the hyperthermia, and histaminergic H_1 and H_2 receptors, but not serotonin, may be involved in the hypothermia.

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